REMARKS

Claims 1-10 and 13-24 were pending in this application when last examined. Claims 1-10, 13-21 and 23-24 have been canceled. Claim 22 has been amended and new claims 25-36 have been added.

Support for the amendments can be found in the specification and original claims as filed. Support for amended claim 22 can be found, for example, in the specification at page 5 and at page 8. Support for new claim 25 can be found, for example, at page 9. Support for new claim 26 can be found, for example, at 6. No new matter has been added.

CLAIM REJECTIONS - 35 USC § 102

At page 5, item 14, the Office Action rejects claims 1-8, 13-21 and 23-24 under 35 U.S.C. § 102(b) as being anticipated by PANKHANIA et al. (WO 02/083119). Applicants respectfully traverse the rejection.

Claims 1-8, 13-21 and 23-24 have been canceled thus rendering this rejection moot. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CLAIM REJECTIONS - 35 USC § 103

At page 7, item 17, the Office Action rejects claims 9-10 and 22 under 35 U.S.C. § 103(a) as being unpatentable

over PANKHANIA, in view of MITRA (WO 95/07103). Applicants respectfully traverse the rejection.

Currently amended claim 22 is directed to a method for locally treating buccopharyngeal ailments in a subject. The method includes providing a composition comprising a non-steroidal anti-inflammatory drug (NSAID) in a water-soluble amino acid salt form, orally and locally administering the composition to the subject, and allowing the composition to solubilize in the buccopharyngeal cavity of the subject. The composition is solubilized by the saliva of the subject, whereby the amino acid dissociates from the NSAID thereby imparting a lipophilic property to the NSAID. The lipophilic NSAID then actively diffuses through the mucous tissues in the buccopharyngeal cavity of the subject without recrystallizing. PANKHANIA and MITRA fail to teach or suggest such a method.

PANKHANIA describes a composition for systemically treating migraine and nausea that includes ibuprofen and prochlorperazine. PANKHANIA discloses that the systemic composition can be administered orally, rectally, parenterally, buccally or topically. Preferably the compositions are in a form "suitable for oral administration or in the form of a suppository." (See, page 4, lines 20-24).

PANKHANIA then describes compositions for oral administration, such as solid compositions (see, page 4, lines 32 to page 5, line 14) and liquid compositions (see, page 7, lines

9-17). PANKHANIA also describes compositions for topical administration (see, page 7, line 19 to page 8, line 2), rectal administration (see, page 8, lines 12-17), and parenteral administration (see, page 8, lines 19-21). Missing from PANKHANIA, however, is any enabling disclosure related to local treatment of buccopharyngeal ailments.

It is known that lipophilic drugs (e.g., NSAID) are hydrophobic and insoluble in the mouth/saliva environment. As a result, the lipophilic molecules remain in the crystalline state and do not dissolve; therefore, the active ingredient cannot be absorbed by the mucous epithelium. Moreover, the acid insoluble crystal forms induce nausea and local irritation when the drug comes in contact with mucous tissue. While PANKHANIA mentions buccal administration of its drug composition, it fails to teach or suggest how to overcome these established problems in order to locally treat buccopharyngeal ailments.

At page 6, the Office Action states that "the composition taught by Pankhania can be retained in the oral cavity and since this composition contains all the structural components of the instant claims, the delivery of the active ingredient across the oral or buccal mucosa will necessarily occur." Also, at page 7, the Office Action states that "Pankhania teaches formulations that will release the active ingredient in the mouth, and the active ingredient will be absorbed through the

oral or buccal mucosa." Applicants respectfully disagree with these conclusions.

PANKHANIA teaches the use of 50 to 800 mg of ibuprofen in each dose (*see*, page 2, lines 28-31). These are high dosages related to a typical systemic application range. These high dosages of ibuprofen, even when as little as the lowest 50 mg dosage, would recrystallize in the mouth environment and thus encounter the problems discussed above. The PANKHANIA composition would not work in a method for locally treating buccopharyngeal ailments. The oral mucosa is a lipophilic epithelium. Thus, it is not possible for a lipophilic drug such as NSAID, in the formulations described in PANKHANIA, to dissolve and coat the mucous without locally recrystallizing. At the doses described, the PANKHANIA composition cannot be solubilized by the saliva of the subject, whereby the lipophilic NSAID then actively diffuses through the mucous tissues in the buccopharyngeal cavity of the subject without recrystallizing, as featured in the presently claimed method.

Applicants have applied a pharmacological rule, i.e., Fick's rule, to the presently claimed methods. This allows for local low dosage and mucous coating to obtain per-mucous absorption and bioavailability of a lipophilic drug. The claimed methods keep the NSAID dissolved in the buccopharyngeal cavity while actively diffusing through the mucous tissues and without

recrystallizing. The compositions described in PANKHANIA cannot accomplish this method.

The Office Action contends that PANKHANIA discloses compositions that effervesce when in contact with water and that an effervescent composition will release the active ingredient (NSAID) in the mouth to be absorbed by the oral/buccal mucosa. The Office Action then concludes that the delivery of active ingredient across the oral or buccal membrane will necessarily occur. Applicants respectfully disagree that such a position can be applied against the presently claimed methods.

As detailed above, the PANKHANIA compositions are formulated to systemically treat a subject. The formulations comprise the high doses of ibuprofen (50 to 800 mg) that are necessary to be pharmacologically effective for treatment through the blood flow. PANKHANIA, however, fails to teach or suggest any method that allows the composition to solubilize in the buccopharyngeal cavity – solubilized by the saliva of the subject – wherein the now lipophilic NSAID then actively diffuses through the mucous tissues in the buccopharyngeal cavity of the subject, without recrystallizing. Indeed, the PANKHANIA composition will not behave in this manner. Moreover, the Office Action has failed to provide any scientific or clinical evidence to corroborate its contention that a formulation intended for systemic administration, such as that described in PANKHANIA, would have

these properties for diffusion into buccal and throat mucous membranes without recrystallizing.

Again, while PANKHANIA mentions buccal administration of its high dose drug composition, PANKHANIA fails to teach or suggest any way to locally treat buccopharyngeal ailments, such as buccal mucous inflammation or sore throat. PANKHANIA's goal is to treat migraine or nausea under a conventional oral route, and also a possible rectal, parenteral, or topical route, but fails to disclose local buccal administration.

MITRA also relates to a systemic compound to be administered by an oral route, with general effects on the body and organs. Like PANKHANIA, MITRA fails to teach or suggest the local buccal administration of a low dosage lipophilic NSAID that locally diffuses into buccal and throat mucous membranes without recrystallizing. In addition, MITRA in combination with PANKHANIA fails to enable one of ordinary skill in the art to make or practice the claimed subject matter.

The Office Action recognizes that MITRA discloses a composition with 50 to 800 mg ibuprofen lysinate. As detailed in the above remarks, even the 50 mg ibuprofen amount, when applied orally and locally, would produce local undesired recrystallization. MITRA fails to teach or suggest anything that would lead one of ordinary skill in the art to use a dosage of NSAID to formulate a composition for locally treating buccopharyngeal ailments, as presently claimed.

Evidence of criticality and unexpected results

Applicants submit herewith duly executed Rule 132 Declarations from the inventors with evidence of the criticality and unexpected results regarding the claimed method. Note that the data contents of the two declarations are identical.

As shown in the Declaration, the presently claimed method of local buccopharyngeal treatment has been studied in clinical trials. In those studies, higher doses of ibuprofen lysinate, e.g., 50 mg per 1000 mg unit (5.0 wt%) was compared to the 25 mg ibuprofen lysinate (2.5 wt%) dose and to placebo. The clinical trial's initial results on 60 patients of 25 mg dose versus placebo were positive. The next question was to evaluate whether these results could be improved by utilizing a higher dose of ibuprofen.

The trial's next study evaluated a 50 mg ibuprofen lysinate dose in a lozenge having a formulation that was otherwise the same as the 25 mg dose. The study revealed that, as detailed in the specification and in the above remarks, the formulation was inadequate for releasing and slowly dissolving the higher 50 mg dose of ibuprofen lysinate. When tested, the 50 mg dose released a locally crystallized amount of ibuprofen that could not be absorbed by the mucous. Although the formulation also included a strong peppermint flavoring, the bad taste led all of the study participants to immediately stop sucking the lozenge, spit it out and then rinse their mouth. The disgusting

ibuprofen taste remained for a long time. These undesired side effects were not present with the 25 mg ibuprofen lysinate dosage.

As evidenced by the clinical trials, the method for locally treating buccopharyngeal ailments as featured in claim 22 would not have been obvious over the mere "oral administration" of the dosage forms taught by both PANKHANIA and MITRA. In contrast to the position stated in the Office Action, a subject provided with a tablet taught by PANKHANIA or MITRA and then retained in the mouth, would not retain the tablet "allowing the composition to solubilize in the buccopharyngeal cavity of the subject" and the ibuprofen would not actively diffuse "through mucous tissues in the buccopharyngeal cavity of the subject without recrystallizing" as recited in present claim 22.

For all of these reasons, the combination of PANKHANIA and MITRA fails to teach or suggest, and would not have rendered obvious, the method for locally treating buccopharyngeal ailments of claim 22. Claims 9 and 10 have been canceled. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

Entry of the above amendments is earnestly solicited. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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HJV/jr

APPENDIX:

The Appendix includes the following item(s):

☒ - a 37 CFR 1.132 Declaration of Marc MAURY

☒ - a 37 CFR 1.132 Declaration of Philippe PEROVITCH